RESPONSE TO DR. CRUMP'S COMMENTARY ON "MULTI-STAGE MODEL ESTIMATES OF LUNG CANCER RISK FROM EXPOSURE TO DIESEL EXHAUST, BASED ON A U.S. RAILROAD WORKER COHORT," BY S.V. DAWSON AND G.V. ALEXEEFF

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We thank Dr. Kenny Crump for his commentary (Crump, 2001) on our article, "Multi-Stage Model Estimates of Lung Cancer Risk from Exposure to Diesel Exhaust, Based on a U.S. Railroad Worker Cohort" (Dawson & Alexeeff, 2001), both of which appeared in the February issue of *Risk Analysis*. This response is to address issues raised in his commentary and to provide supplemental information as requested in his comment. We appreciate his general remarks regarding the extensive evaluation that the Garshick et al. (1998) railroad worker cohort has undergone. We agree that it is important for other investigators to re-evaluate existing complex data sets. We add that it is important to evaluate this study not only on its own but also in the context of the results from many other positive epidemiological studies of the carcinogenicity of diesel exhaust (Cal/EPA, 1998).

The intent of our work on the health risks of diesel exhaust has been to provide information that would promote public health. The context of the results of other epidemiological studies has helped motivate our emphasis on providing estimates of positive trends of lung cancer risk with increasing exposure to diesel exhaust in our analysis of the railroad cohort. The risks calculated in our paper are consistent with the results of those other studies and analyses (Table I).

Following his general remarks, Dr. Crump's commentary has a brief account of several analyses of the Garshick et al. (1988) railroad worker cohort study. We endeavor to clarify two points in that account. The first concerns the diesel-exhaust exposure experienced by the shop workers. The second is the statement that the HEI panel's report (1999) contained a critique of the multistage analysis. Dr. Crump goes on to raise three points that directly question the analysis in our paper. The first is that our parametric control for age, derived from the multistage model, may not be appropriate. The second is that our next-to-last-stage analysis should have excluded the unexposed workers. The third is his

concern about the biological plausibility of our last-stage model. We respond to each of these five points in turn.

Shop worker exposure.

Dr. Crump asserts that even though some jobs held by shop workers did not involve diesel exhaust exposure, shop workers as a group had considerably higher diesel-exhaust exposures than train riders. However, he does not provide any evidence that the exposure of shop workers as a group was considerably higher. As we point out in our paper, some shop workers did have measured exposures that were considerably higher than workers riding trains, but no data have been made available about how many there were. Other shop workers had virtually no exposure. For the last-stage model, our paper addressed this issue by performing a sensitivity analysis that includes shop workers and brackets the exposure of the shop workers as a group. The result of the sensitivity analysis is that the inclusion of the shop workers does reduce the exposure slope. The statistical significance of the slope is also reduced. When we assume that that half the shop workers were exposed to the higher concentration, the exposure slope is reduced by 19% but is still highly significant ($p = 0.0005$). Only when we make the extreme assumption that all shop workers were exposed to the considerably higher concentration is the slope reduced by a substantial factor, 3.5, and the slope becomes marginally insignificant ($p = 0.055$-0.066). The inclusion of the unexposed shop workers with the workers assigned the higher exposure evidently dilutes the cancer risk attributable to diesel exhaust.

The HEI panel's report on the multistage model.

Dr. Crump asserts that the HEI panel's report (1999) contained a critique of the multistage analysis. The only issue raised about the multistage model that we could find in that report is on page 59, column 2: "This multi-stage model is likely to have the same difficulties with cumulative exposure as were pointed out in the discussion of models 5 and 7." That statement refers to a result in the HEI panel's report that excluding the unexposed group from the exposure-response relationship causes the

significant positive exposure slope to become insignificantly negative, a point later mentioned in Dr. Crump's commentary.

Because the HEI panel's report made only this unsupported statement about multi-stage models, it seems a stretch to say that the panel report contained a critique of the multistage analysis. Furthermore, not only is the HEI panel's statement unsupported, it is contradicted by our paper's report of finding a significant positive exposure slope for the last-stage model with the unexposed workers excluded. Our statistical finding is consistent with the trend shown in Fig. 4 of our paper, and Dr. Crump's commentary affirms this point when he states that the exposure-response trend appears positive even within train riders. Consequently we believe that the HEI panel's report should not be said to critique the multi-stage analysis we conducted.

Control of the covariates.

Dr. Crump states that lack of control of age and other variables in the model can produce spurious positive exposure-related trends. He then reports that our parametric model using age as a continuous variable in a power law derived from the multistage model does not describe the age relationship in the Garshick et al. (1988) data very well. His reasoning was that when he replaced the continuous variable with a categorical variable, he obtained a highly significant improvement in fit.

Appropriate use of controls for age and other variables is very important in analysis of studies such as this one. We explored several covariate structures to implement the most satisfactory controls for age and related variables. In this response we use only 5-year age intervals when categorizing the age and year variables in order to characterize their variation adequately.

Our response to Dr. Crump's report of using an alternate approach in order to obtain a better fit starts by looking at the age-dependence of cancer rates among the unexposed workers in the cohort. The figure below shows on a log-log plot the trends for unexposed workers in each of the birth cohorts in the study. The trends approximate straight lines, with noise and some nonsignificant bending ($p > 0.5$).

The slope of the lines is about 6, which is the power for the 7-stage model calculated in our work. We use a chi-squared distribution of deviance to characterize fit in these remarks. The fit of the continuous variable (straight line on the plot) is reasonable ($p = 0.04$), considering that the population is heterogeneous and the analysis uses a homogeneous Poisson model. Furthermore, we obtain no significant improvement in fit when the continuous age variable is replaced with a categorical variable ($p = 0.30$).

Next, we look at the fit for an analysis including both exposed workers (on trains) and unexposed workers. Contrary to Dr. Crump's result, using a next-to-last-stage model with calendar year (in 3-year intervals) as an additional covariate, we obtain no significant improvement in fit when the continuous age variable is replaced with a categorical variable ($p = 0.25$). In fact results for our next-to-last-stage model with birth year as an additional categorical covariate (in 5-year intervals) show that the fit obtained for the categorical age variable is actually worse than for our parametric approach using power of age. For the last-stage model we obtain similar results that the categorical age variable does not improve the fit. Consequently we find that the parametric form of the multistage model provides a better approach than the proposed categorical approach.

With regard to Dr. Crump's question about how sensitive the exposure-response trends are to the choice of covariates for the next-to-last-stage model, use of the categorical age variable reduces the exposure slopes somewhat, relative to the parametric approach. However, when we use both age and another time-related covariate, we get different results depending on which covariate we include with age. When we include calendar year as an additional covariate, the exposure slope for the categorical age variable is 37% lower than for the parametric approach, and the slope becomes marginally insignificant ($p = 0.067$). When instead we include birth year as an additional covariate, the exposure slope for the categorical age variable is 25% lower than for the parametric approach but remains significant ($p = 0.019$). Whether we use calendar year or birth year as an additional covariate, the exposure slopes for the parametric approach for age dependence are both highly significant ($p = 0.004$ and $p = 0.003$, respectively). Evidently the flexibility of the categorical age variable leads to the reduction of significance of the exposure slopes, especially for use of the calendar-year covariate, which

is correlated with the age variables. We think the correlation of the age variable with calendar year is an argument for preferring birth year as the additional covariate, and this choice leads to a reduction of the statistical uncertainty of the slope estimate.

Inclusion of unexposed group in the analysis

Dr. Crump states that inclusion of clerks and signalmen as an unexposed group in the analysis can produce spurious positive exposure-related trends. He asserts that the unexposed workers should be excluded because they have a lower cancer rate as a group than exposed workers. Earlier in his commentary he refers to his work (1999) suggesting that the elevated cancer rates of the exposed workers were likely due to uncontrolled life style factors. He points out that considering only the exposed workers with a next-to-last-stage model appears to result in negative exposure-response trends.

The exclusion of the unexposed group from determining the exposure-response relationship requires substantial justification. We use what must be a far more common assumption in epidemiological analysis that the unexposed group should be assigned a relative risk of 1 and included in the exposure response. Our paper has a discussion of possible effects of differential smoking, the usual life-style confounder for lung cancer studies. We find that reasonable assumptions about smoking prevalence are unlikely to explain the elevated cancer rates of the exposed workers. So we have a fundamental disagreement. We acknowledge that the exclusion of the unexposed workers in the case of the next-to-last-stage model results in exposure slopes that may not be positive. This is not, however, true of the last-stage model.

In the sensitivity analysis of our paper we do not report the values of slopes for the exposure responses that excluded the unexposed workers because the actual values do not seem useful. But in response to the commentary we now report the values obtained by excluding the unexposed workers and using the roof exposure pattern in the next-to-last-stage model. With birth year as an additional covariate we calculate the slope, - 0.0042 (corrected for intermittency), not statistically significant ($p = 0.4$). With

calendar year instead of birth year as an additional covariate, we calculate the slope, - 0.0030, marginally insignificant ($p = 0.06$).

Although the analysis excluding the unexposed workers provides a potentially useful perspective, we think that, on balance, it is most important to consider exposed and unexposed workers together in examining the shape of exposure-response trends and in estimating exposure slopes, which then become significantly positive for the next-to-last-stage model. Our paper suggests an explanation of the shape of the exposure response, with a rise at the beginning and a downturn for longer exposures. This explanation is based on a sensitive subpopulation, as proposed for the effect of smoking (Xu et al. 1996). But in view of the uncertainties and as a pragmatic result, we think it is still important to report the unit risks for the simple overall exposure slopes.

Last-stage model

Dr. Crump points out that for the last-stage model the exposure-response trend appears positive even with the unexposed workers not included in the dose response. He states that this particular version of the multistage model has a peculiar form, in that it predicts that mortality is solely a function of exposure exactly ten years earlier, and totally independent of previous or later exposures. He goes on to state that the way exposure appears in the last-stage model does not appear very biologically plausible to him. He would also like to see how sensitive this analysis is to the way that age and calendar year are controlled.

The statement concerning the exact ten-year lag from exposure to death is a typical simplifying statement for the mathematical modeling. In reality the exposure is an average over one year and the ten-year lag is essentially the average of a distribution for lag times. Use of an average lag is of the same character as the assumption for lag time in the models of the other analyses of this study and is common in the analysis of epidemiological data.

In considering biological plausibility we note that an essential element of modern cancer models is the transformation of cells from normal to malignant, generally through serial intermediate transformations. All of these models have a final transition to malignancy. If that transition is influenced by a particular exposure, then we have a last-stage model, and the influence on the rate of transition can be approximated as being proportional to the exposure intensity. Though specific identification of a last-stage process has apparently not been reported, we have found no reason, biological or otherwise, why this should not happen in the way the fit of the model to the data suggests.

In response to the query about sensitivity, we report a brief sensitivity analysis for the covariates in a last-stage model, using the same approach as for the next-to-last-stage model above. We find that the last-stage model is even less sensitive to the detailed covariate structure than the next-to-last-stage model. With birth year as an additional covariate we calculate that the exposure slope using the categorical age variable is 5% lower than using the parametric approach and is highly significant ($p < 0.001$). With calendar year as an additional covariate instead of birth year, we calculate that the exposure slope using the categorical age variable is 12% lower than using the parametric approach and is significant ($p = 0.005$). Using the parametric approach, the exposure slopes, 0.0076 and 0.0060 (corrected for intermittency), respectively for the two different additional covariates, are both highly significant ($p < 0.001$). The fit for both these choices of additional covariate is adequate ($p = 0.07$).

Conclusion

Dr. Crump recommends that all the past analyses should be carefully considered in developing a quantitative risk assessment. We believe we did so in Cal/EPA (1998) and in writing our paper although we reject several conclusions from others, especially that the Garshick et al. (1988) cohort study is not suitable for risk assessment. We find that, it is not appropriate to exclude the unexposed workers from the exposure response, nor is it appropriate to omit the last-stage model on the grounds that it may not be biologically plausible. While these are valid points to raise, we do not think the critiques in the commentary invalidate our approach to quantitative risk assessment.

In the face of considerable uncertainties, the assumptions in our paper involve judgement. We maintain that where risk numbers are needed, as they are in California procedures for identifying toxic air contaminants, our upper confidence limits are appropriately health protective in that our assumptions permit the estimation of reasonable upper values for human risk.

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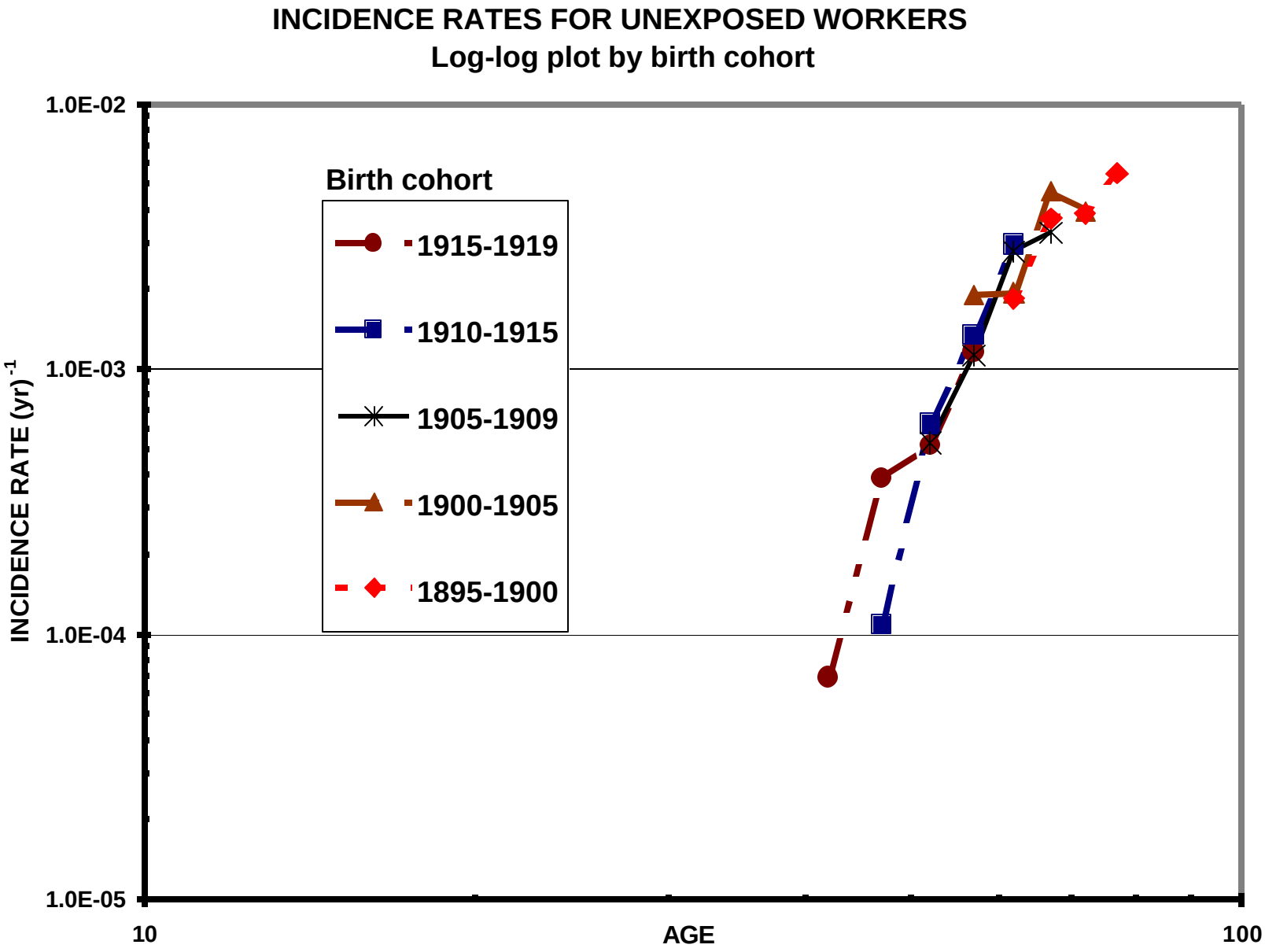
TABLE 1 COMPARISON OF UNIT RISKS FOR DIESEL EXHAUST

Study population. Health and exposure data sources	**Hazard assessment reference**	**Expression of risk slope in the hazard assessment reference**	**Unit risk** [70 yr-(μg ambient particles/m^3)]$^{-1}$
London transport workers Waller (1981)	Harris *et al*. (1983)	5×10^{-4} (yr-μg/m^3)$^{-1}$ [b]	1.4×10^{-3} [a b]
Smoking-adjusted Pooled Relative Risk	Smith (1998)	3×10^{-4} [70 yr-(μg ambient particles/m^3)]$^{-1}$	3×10^{-4}
U.S. railroad workers case-control study Garshick *et al*. (1987)	McClellan *et al*. (1990), Mauderly (1992) Stayner (1998)	950 and 3800 [a c] deaths/yr in the U.S. 1.5×10^{-4} and 7.1×10^{-4} (45 yr-μg /m^3)$^{-1}$ [c]	2.9×10^{-4} and 1.2×10^{-3} [a c] . 7.1×10^{-4} and 3.3×10^{-3} [c f]
U.S. truck drivers Steenland *et al*. (1990), Zaebst *et al*. (1991)	Steenland *et al*. (1998)	2.3×10^{-4} to 8.1×10^{-4} [c d], 6.1×10^{-4} [a e] (45 yr-μg elemental carbon/m^3)$^{-1}$	4.0×10^{-4} to 1.5×10^{-3} [c f], 1.1×10^{-3} [a e f]
Meta-analysis Cal/EPA (1998)	Cal/EPA (1998)	Relative risk = 1.57 [a]	1.6×10^{-4} to 1.2×10^{-3} [a c]
U.S. railroad workers Garshick *et al*. (1987, 1988), Woskie *et al*. (1988a, 1988b)	Cal/EPA (1998) Empirical, cohort Multi-stage, cohort; Case control	4.4×10^{-4} (yr-μg/m^3)$^{-1}$ [a h], $R_1 = 8.3 \times 10^{-3}$ (μg/m^3)$^{-1}$ [a i], 0.037 yr^{-1} [a l]	1.3×10^{-4} to 2.4×10^{-3} [a k l]
U.S. railroad workers Garshick *et al*. (1988), Woskie *et al*. (1988a, 1988b)	Dawson *et al*.(2001) Multi-stage, cohort	$R_1 = 8.3 \times 10^{-3}$ to 2.4×10^{-2} (μg/m^3)$^{-1}$ [a j]	2.1×10^{-4} to 5.5×10^{-4} [a k l]

a. 95% upper confidence limit.
b. This hazard is not statistically significant.

Table 1 (continued)

c. Range based on an upper and a lower concentration assumption.
d. Maximum likelihood estimates.
e. Obtained from the exposure coefficient 3.5×10^{-4} with standard error 1.55×10^{-4}.for the best value of exposure.
f. Multiplies value in cell to the left by (70/45)/0.33 = 4.7 to adjust respectively for working years and intermittency.
g. Multiplies value in cell to the left by (70/45)/0.33 x 0.40 = 1.9 to adjust respectively for working years, intermittency and an elemental carbon content of 40% in the diesel exhaust particles.
h. This is the highest slope for the empirical models, based on the ramp exposure pattern. It yields the top of the range of unit risk.
i. This is the lowest slope for multi-stage models, based on the roof exposure pattern. It yields the bottom of the range of unit risk.
j. Range based on different models and exposure assumptions.
k. Uses a California life table procedure with the exposure slope in the cell to the left.
l. Used with exposure assumption, roof or ramp.


INCIDENCE RATES FOR UNEXPOSED WORKERS
Log-log plot by birth cohort
1.0E-02
1.0E-03
1.0E-04
1.0E-05
INCIDENCE RATE (yr)-1
Birth cohort
1915-1919
1910-1915
1905-1909
1900-1905
1895-1900
10
AGE
100